

Epidemiology and treatment of gonorrhoea caused by penicillinase-producing strains in Liverpool

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SUMMARY The epidemiological features are described of an outbreak of gonorrhoea caused by penicillinase-producing strains of gonococci in 76 patients in Liverpool between February and November 1976. Initially infections were confined to a socially deprived inner city area with a large immigrant population, and subsequent spread of infection remained circumscribed. The characteristics of those patients acquiring these infections were similar to those infected by gonococci of diminished sensitivity to benzylpenicillin, and showed a strong association with adverse social factors. A comparison of the clinical features of patients harbouring sensitive, less sensitive, and penicillinase-producing strains showed severe symptoms and signs in men and a greater involvement of multiple sites in women infected with penicillinase-producing gonococci. Treatment with penicillins failed. Tetracycline was satisfactory in men but was less so in women in whom gonococci persisted in the rectum. Cefuroxime and spectinomycin were effective.

Introduction

Penicillinase-producing gonococci appeared in Liverpool in February 1976 (Percival *et al.*, 1976; Turner *et al.*, 1976) and, simultaneously, in the Far East (Ashford *et al.*, 1976). Subsequently, they were recognised in a patient infected in West Africa (Piot, 1977). Liverpool strains have spread to other parts of the United Kingdom (Wilkinson *et al.*, 1976), Grays, Essex (Wisdom, 1977, personal communication), and Chichester (Warren-Browne, 1976, personal communication). As well as becoming established in North America (Center for Disease Control, 1977), strains from the Far East have spread to many other countries including Australia, Canada, Japan, Netherlands (Blog *et al.*, 1977), New Zealand, Norway, Philippines, Republic of Korea, and Singapore (Center for Disease Control, 1977). Earlier, the World Health Organisation warned doctors and laboratories of this development and issued recommendations for the surveillance of β -lactamase-producing gonococci (World Health Organisation, 1976).

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The discovery of these strains carries grave implications (*British Medical Journal*, 1976; *Lancet*, 1976). Poor countries, especially, may lack the basic facilities required for their recognition and find their treatment expensive.

Some of our initial observations have been reported (Percival *et al.*, 1976). Here, we describe the epidemiological and clinical features of the outbreak in Liverpool, its development and control, and the response to treatment of patients infected by β -lactamase-producing gonococci.

Materials and methods

Every venereologist and bacteriologist in the sexually transmitted disease service in Liverpool and Birkenhead participated in the study. The clinics were those at the Liverpool Royal Infirmary, the Seamen's Dispensary, and St James' Hospital, Birkenhead. The clinical and epidemiological details of patients infected by β -lactamase-producing gonococci seen between February 1976 and 15 November 1976 are presented, and compared with prospectively collected data for patients with non-penicillinase-producing gonococci seen between 15 August and 15 November 1976. For comparison

the non-penicillinase-producing strains are divided into two categories: those with minimum inhibitory concentrations (MICs) of benzyl penicillin of less than 0.125 units per ml, designated as 'sensitive', and those with MICs of 0.125 units per ml or above, designated as 'less sensitive'. All information was recorded on proformas. The significance of differences was determined by the χ^2 test.

The laboratory methods have been described elsewhere (Percival *et al.*, 1976; Turner *et al.*, 1976). The usual treatment for uncomplicated gonorrhoea, as soon as the provisional diagnosis based on the results from stains of genital secretions was made but before the results of culture were available, was procaine penicillin, 1.2 megaunits intramuscularly (i.m.), supplemented orally by either ampicillin 1 g, talampicillin 1 g, or amoxycillin 0.5 g or 1 g. For those who were allergic to penicillin and those in whom initial treatment failed, one of the following regimens was given: erythromycin or tetracycline 500 mg orally six hourly for 5 to 7 days, spectinomycin 2 g i.m. for men and 2 g or 4 g i.m. for women, kanamycin 2 g i.m., or co-trimoxazole four tablets twice daily for two days. From the middle of October, cefuroxime in a single dose of 1 g i.m. was used. Cure of infection was judged by negative culture at least twice, and usually three times, during three weeks after the end of treatment. In women this included rectal as well as urethral and cervical cultures.

Results

At two of the three clinics (Liverpool Royal Infirmary and the Seamen's Dispensary), 408 patients were studied. There were 267 men, including 44 with penicillinase-producing isolates, and 141 women, including 32 with enzyme positive isolates. The findings at the third clinic (St James' Hospital, Birkenhead), serving the Wirral, are described separately.

EPIDEMIOLOGY

Age and marital state

There were no significant differences in age or marital state between the three groups.

In Tables 1, 2, and 3, a number of epidemiological characteristics are presented for men and women separately, according to the sensitivity to benzylpenicillin of the gonococci isolated. The contingency tables with their χ^2 values are shown separately. Those for whom the relevant information was not available are excluded from the calculations of percentages and χ^2 values. The contingency tables relating to Table 1 are designated as Tables 1a, 1b, and 1c, the table relating to Table 2 is

designated as Table 2a, and those relating to Table 3 are labelled consecutively from Table 3a to Table 3h.

Race (Tables 1 and 1a)

Of the β -lactamase positive isolates 76% were from Black and only 18% were from White men. This ratio was almost completely reversed among 'sensitive' isolates with 17% from Blacks and 76% from Whites. This difference was highly significant ($P < 0.001$). In contrast, only a few women in all three groups were Black.

History of gonorrhoea (Tables 1 and 1b) and no. of consorts (Tables 1 and 1c)

In men there were significant differences between those with penicillinase-producing and 'sensitive'

Table 1 *Epidemiological characteristics of patients related to sensitivity to benzylpenicillin of infecting gonococci*

Characteristics	No. positive related to sensitivity of isolate*					
	β -Lactamase negative				β -Lactamase positive	
	Sensitive		Less Sensitive			
	Male	Female	Male	Female	Male	Female
	No. %	No. %	No. %	No. %	No. %	No. %
Race						
White	117 76	68 91	33 48	28 90	6 18	14 93
Black	27 17	4 5	33 48	3 10	26 76	1 7
Coloured	11 7	3 4	2 3	—	2 6	—
Not known	—	3 —	—	—	10 —	17 —
Previous gonorrhoea	42 28	13 17	23 38	5 16	22 50	7 22
Consorts						
2 or more	46 30	14 18	21 32	5 16	19 54	10 33
No. studied in each category	155	78	68	31	44	32

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml
Less sensitive = MIC 0.125 units/ml or above

Table 2 *Occupation of patients related to sensitivity to benzylpenicillin of infecting gonococci*

Occupation	No. positive related to sensitivity of isolate*					
	β -Lactamase negative				β -Lactamase positive	
	Sensitive		Less sensitive			
	Male	Female	Male	Female	Male	Female
	No. %	No. %	No. %	No. %	No. %	No. %
Skilled or professional	53 34	20 26	15 22	7 23	9 20	6 19
Unskilled or unemployed	50 32	33 42	22 33	13 42	26 59	12 37
Student	12 8	5 6	6 9	1 3	5 11	2 6
Seaman	19 12	—	18 27	—	1 2	—
At home	—	20 26	—	10 32	—	12 38
Others	21 14	—	7 10	—	3 7	—
No. in each category	155	78	68	31	44	32

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml
Less sensitive = MIC 0.125 units/ml or above

Table 3 *Residence of patients and consorts related to sensitivity to benzylpenicillin of infecting gonococci*

Residence	No. positive related to sensitivity of isolate*					
	β -Lactamase negative				β -Lactamase positive	
	Sensitive		Less sensitive			
	Male	Female	Male	Female	Male	Female
No. %	No. %	No. %	No. %	No. %	No. %	No. %
Of patients						
Liverpool 7 and 8	29 19	12 15	29 43	16 52	25 57	16 50
Other						
Liverpool	93 60	56 72	21 31	14 45	16 36	16 50
Wirral	7 4	7 9	2 3	—	1 2	—
UK	14 9	3 4	3 4	1 3	1 2	—
Foreign	12 8	—	13 19	—	1 2	—
Of consorts or meeting place						
Liverpool 7 or 8	11 7	12 16	29 43	15 50	11 33	16 55
Other						
Liverpool	90 58	48 66	26 38	13 42	17 52	10 35
Wirral	4 3	5 7	—	—	—	1 3
UK	34 22	8 11	4 6	2 7	4 12	1 3
Foreign	16 10	—	9 13	—	1 3	1 3
Liverpool unspecified	—	5 —	0 —	1 —	11 —	3 —
No. in each category	155	78	68	31	44	32

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml
 Less sensitive = MIC 0.125 units/ml or above

Contingency tables 1a–3d *Comparisons between patients infected by β -lactamase producing and sensitive gonococci*

Epidemiological characteristics	No. positive related to sensitivity of isolate*		χ^2 with Yates's correction	P
	Sensitive	β -Lactamase +		
Race (men) (Table 1a)				
White	117	6	45.67	<0.001
Black	27	26		
Previous gonorrhoea (men) (Table 1b)				
Yes	42	22	6.34	<0.02
No	107	22		
No. of consorts (men) (Table 1c)				
2 or more	46	19	6.08	<0.02
Less than 2	105	16		
Occupation (men) (Table 2a)				
Unskilled or unemployed	50	26	9.35	<0.01
Others	105	18		
Patient's residence				
Men (Table 3a)				
Liverpool 7 and 8	29	25	23.28	<0.001
Others	126	19		
Women (Table 3b)				
Liverpool 7 and 8	12	16	12.56	<0.001
Others	66	16		
Consort's residence or meeting place				
Men (Table 3c)				
Liverpool 7 and 8	11	11	15.68	<0.001
Others	144	22		
Women (Table 3d)				
Liverpool 7 and 8	12	16	13.75	<0.001
Others	61	13		

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml

isolates with respect to history of gonorrhoea (50% compared with 28%, $P < 0.02$) and having two or more consorts during the three weeks before attending the clinic (54% compared with 30%, $P < 0.02$).

Occupation (Tables 2 and 2a)

Many of the men infected by enzyme positive gonococci were unskilled or unemployed (59%) compared with those infected by 'sensitive' gonococci (32%, $P < 0.01$). Only one of the men with enzyme positive isolates was a seaman. Five were students, all being foreigners from Africa or the Middle East but living in Liverpool.

Residence of patients (Tables 3, 3a, 3b, 3e, and 3f)

A high proportion of both enzyme positive and 'less sensitive' isolates occurred in men and women who lived in only two (7 and 8) of the 36 districts of Liverpool and adjacent areas. Thus, approximately half of all isolates in these two groups were found in such patients, but only 15% and 19% respectively for women and men with 'sensitive' isolates ($P < 0.001$). Only two men with penicillinase-producing isolates came from outside the Liverpool area; one, a West Indian from Birmingham, had acquired his infection in Liverpool and the other, a seaman from Ghana, claimed to have last had sexual intercourse in Germany. He arrived in Liverpool at least a week after the discovery of the other patients with enzyme positive gonococci.

Contingency tables 3e–3h *Comparisons between patients infected by sensitive and less sensitive gonococci*

Epidemiological characteristics	No. positive related to sensitivity of isolate*		χ^2 with Yates's correction	P
	Sensitive	Less sensitive		
Patient's residence				
Men (Table 3e)				
Liverpool 7 and 8	29	29	12.86	<0.001
Others	126	39		
Women (Table 3f)				
Liverpool 7 and 8	12	16	13.41	<0.001
Others	66	15		
Consort's residence or meeting place				
Men (Table 3g)				
Liverpool 7 and 8	11	29	38.20	<0.001
Others	144	39		
Women (Table 3h)				
Liverpool 7 and 8	12	15	10.71	<0.01
Others	61	15		

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml
 Less sensitive = MIC of benzylpenicillin 0.125 units/ml or above

Residence of consorts or meeting place (Tables 3, 3c, 3d, 3g, and 3h)

The same differences were observed in consorts' address or meeting place. For men, 33% of consorts

of those infected by enzyme positive isolates and 43% of those with 'less sensitive' isolates, but only 7% of those with 'sensitive' isolates either lived or were met in Liverpool 7 or 8 (respectively, $P < 0.001$ and $P < 0.001$). For women, the corresponding figures were, 55%, 50%, and 16% (respectively $P < 0.001$ and $P < 0.01$). Two women infected by penicillinase-producing gonococci in March 1976, had additional consorts in London, York, and Chichester. These consorts had failed treatment with penicillin without recognition of penicillinase production. Four men infected in Liverpool had additional consorts elsewhere, three in London and one in Middlesbrough.

One club, used by non-Whites, was often named as the meeting place for those with 'less sensitive' and penicillinase-producing gonococci.

Sixteen per cent of the women infected by enzyme positive gonococci, all unmarried, but only 4% of those with 'sensitive' gonococci were pregnant when first seen, suggesting a less responsible approach to contraception in the former category.

CLINICAL FEATURES

The clinical features on first presentation for men are shown in Table 4 and for women in Table 5. In men the only significant difference was the higher incidence (23%) of enlarged tender inguinal lymph glands in those infected by enzyme positive gonococci than in either of the other two categories (2 and 4%, $P < 0.001$). In women, penicillinase-producing gonococci were more often isolated from each site and from multiple sites and associated with

Table 5 *Clinical features in women related to sensitivity to benzylpenicillin of infecting isolate*

Clinical features	No. positive related to sensitivity of isolate*					
	β -Lactamase negative				β -Lactamase positive	
	Sensitive		Less sensitive			
	No.	%	No.	%	No.	%
Symptoms						
None	40	51	9	29	18	56
Discharge	15	19	8	26	6	19
Abdominal pain	10	13	7	23	5	16
Others	13	17	7	23	3	9
Duration						
< 1 week	10	26	5	23	7	50
1 to 2 weeks	15	39	10	45	2	14
≥ 3 weeks	13	34	7	32	5	36
Signs						
None	25	32	10	32	11	34
Cervicitis	16	20	3	10	3	9
Ubr†	6	8	3	10	4	12
Multiple	16	20	9	29	7	22
Salpingitis	8	10	4	13	5	16
Others	7	9	2	6	2	6
Positive culture						
Cervix	68	87	25	81	30	94
Urethra	50	64	23	74	27	84
Rectum	26/57	46	16/25	64	12/20	60
For trichomoniasis	9	12	6	19	8	25
No. in each category	78		31		32	

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml

Less sensitive = MIC 0.125 units/ml or above

†Ubr = mucopus in the urethra or Bartholin duct or rectum

trichomonal infection than in the other two groups, but the differences were not statistically significant.

Only one patient, a man infected by a penicillinase-producing gonococcus, developed disseminated infection characterised by rash and arthritis, three days after treatment with penicillin.

RESPONSE TO TREATMENT

In assessing response to treatment, the usual difficulty of distinguishing relapse from reinfection was even greater for those with penicillinase-producing isolates because of what appeared to be the higher level of promiscuity. Table 6 shows the response to the various treatments in those adequately followed-up. Those considered reinfected and a patient with a penicillinase-positive isolate who received further medication from a doctor for bronchitis are excluded.

Men

There were only three (2.7%) of 110 with sensitive strains and six (14.3%) of 42 with less sensitive isolates who failed treatment with penicillins. One of the latter might have had a penicillinase-positive infection unrecognised in the laboratory, because this was observed in his consort. In the penicillinase-positive group, 36 (95%) of 38 treatments failed. One of the remaining two patients was treated for post-gonococcal urethritis, without further culture

Table 4 *Clinical features in men related to sensitivity to benzylpenicillin of infecting gonococci*

Clinical features	No. positive related to sensitivity of isolate*					
	β -Lactamase negative				β -Lactamase positive	
	Sensitive		Less sensitive			
	No.	%	No.	%	No.	%
Symptoms						
Discharge	84	54	36	53	24	55
Discharge + dysuria	57	37	27	40	20	45
Others	9	6	3	4	—	—
None	5	3	2	3	—	—
Duration						
< 1 week	121	81	56	85	38	86
1 to 2 weeks	26	17	10	15	5	11
≥ 3 weeks	3	2	—	—	1	2
Signs						
Purulent discharge	136	88	61	90	29	66
Discharge + inguinal lymphadenopathy	3	2†	3	4	10	23†
No. in each category	155		68		44	

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml

Less sensitive = MIC 0.125 units/ml or above

† $\chi^2 = 20.9$ $P < 0.001$

Table 6 Results of treatment related to sensitivity to benzylpenicillin of infecting gonococci

Treatment†	β -Lactamase negative*				β -Lactamase positive	
	Sensitive		Less sensitive		Followed	Failed
	Followed	Failed	Followed	Failed		
Penicillins						
Men	110	3 (2.7%)	42	6 (14%)	38	36 (95%)
Women	52	1 (1.9%)	18	0	18	17 (94%)
Tetracycline						
Men	9	0	1	0	9	0
Women	16	2 (12.5%)	5	1	10	3 (30%)
Spectinomycin						
Men	4	1	6	0	18	1 (5.5%)
Women	1	0	0		5	0
Erythromycin						
Men	0		1	0	2	2
Women	1	0	0		6	1
Kanamycin						
Men	0		1	0	0	
Women	2	0	0		1	0
Cefuroxime						
Women	0		0		8	0
Co-trimoxazole						
Men	2	1	0		2	0

*Sensitive = MIC of benzylpenicillin below 0.125 units/ml

Less sensitive = MIC of benzylpenicillin 0.125 units/ml or above

†See text for details

because the smear was negative. The other remained apparently cured for up to two weeks after treatment and then he defaulted.

The number of patients treated with the other regimens was small. For all three categories of gonococci, only two of 28 patients failed treatment with spectinomycin and none of 19 with tetracycline. Both patients with penicillinase-positive isolates who received erythromycin failed treatment.

Women

For patients with enzyme negative isolates, penicillins gave better results in women than men. One patient with an apparent cure among the penicillinase-positive patients was given a course of tetracycline at her second visit, before her negative culture result became known. With tetracycline, five of the six failures, including three with penicillinase-positive isolates, were persistently positive only in the rectum. It is possible there were two more failures in the penicillinase-positive group. Repeated follow-up tests showed the strains to be enzyme negative suggesting reinfection, but the possibility of loss of the penicillinase determining plasmids by the infecting organism could not be excluded. Eight patients harbouring penicillinase-positive strains were cured with cefuroxime. These included a woman with salpingitis who was treated successfully with cefuroxime 0.5 g every eight hours for five days.

FINDINGS AT BIRKENHEAD

Only three of 61 patients studied at St James' Hospital, Birkenhead, were proved to be harbouring penicillinase-producing gonococci. The first, a woman, was seen on 25 October 1976. All three failed treatment with penicillins, but one responded to spectinomycin and the other two to cefuroxime.

Discussion

EPIDEMIOLOGY

In this study, penicillinase-producing gonococci in men were generally in those aged between 20 and 29 years old, who were Black and single. In addition either the patient or his consort lived in or frequented clubs in Liverpool 7 or 8. He was unskilled, unemployed, promiscuous, and had had gonorrhoea once or more in the past. Women with enzyme positive isolates were usually aged between 15 and 29 years, and were White, single or separated. The patient or her consort lived in or frequented clubs in Liverpool 7 or 8, did not regularly practise contraception, was unemployed, promiscuous (although not the same extent as the man), and cohabited with known consorts. She was likely to default and was evasive.

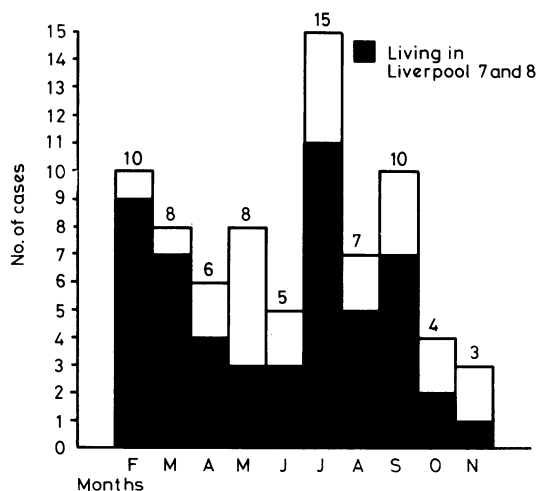


Figure Monthly distribution of cases

The figure shows the total monthly distribution of patients with penicillinase-positive isolates and the proportion of those who lived or acquired their infection in Liverpool 7 or 8. Penicillinase-positive isolates appeared in early February 1976. There were 10 infected patients that month and nine of them lived in Liverpool 7 or 8. Their consorts also either lived in or were met in clubs in the same area (apart from an additional consort in London).

They either presented later or were not seen at all. The remaining patient was the Ghanaian sailor who denied having sexual intercourse in Liverpool and arrived at least one week after the first patients with penicillinase-producing gonococci were seen. Many of the same characteristics were common to those harbouring the less sensitive isolates. These observations show that, in Liverpool, the occurrence of most gonococcal infections is relatively circumscribed, affecting members from the same areas with similar social backgrounds and recreational meeting places. Association of coloured immigrants with a high incidence of gonorrhoea in the United Kingdom (Willcox, 1966; Oller and Wood, 1970) and association with high penicillin MICs (Silver and Darling, 1971) have been noted.

Remarkably, it was eight months before an enzyme positive isolate was found in Birkenhead, separated from Liverpool by only the Mersey River. However, patients attending this clinic differed from those seen in Liverpool. Only one coloured man with a local address had gonorrhoea during the study period. His strain was reported to be sensitive to penicillin but this drug failed to cure his infection. His recent consort proved to be harbouring a penicillinase-positive gonococcus and had earlier had sexual intercourse at a party in Liverpool 8. The female partner of the other two patients in Birkenhead was known to have had gonorrhoea at least twice before and she had associations with Liverpool 8. While 30% of the isolates in Liverpool were 'less sensitive' to benzylpenicillin, only 12% of those at Birkenhead were in this category.

Large towns generally have areas where venereal disease is prevalent. Liverpool is clearly no exception, with some clubs in the inner city being places of high risk. Liverpool 8, especially, contains large areas that have the worst social conditions in the city (Department of the Environment, 1977; Liverpool City Planning Officer 1977, personal communication). The characteristics are those of multiple deprivation—including high rates of sickness and infectious diseases, overcrowding, large families, many immigrants, a large number of people aged between 15 and 24, long-term unemployment, job instability, high rates of infant mortality, illegitimacy and delinquency, and the issuing of supervision orders.

Less frequently the penicillinase-producing gonococci escaped from Liverpool. Two women who defaulted had allegedly been commuting between Glasgow and London via Liverpool. As a result at least one man, a Black seaman who was seen at the Seamen's Dispensary at the end of November 1976, seemed to have acquired a

penicillinase-producing gonococcus in Glasgow. Another woman, presenting in February 1977, claimed to have acquired the infection in London from a seaman recently returned from the Far East and she denied further sexual intercourse for three weeks, but spermatozoa were observed in the vaginal smear. Such an instance illustrates the well-known unreliability of some patients' information and the impossibility of determining the origin of the penicillinase-producing gonococci in Liverpool without epidemiological markers for the isolated gonococci.

ORIGIN OF THE PENICILLINASE-PRODUCING GONOCOCCI ISOLATED IN LIVERPOOL

Except for the Ghanaian sailor (the only seaman), all patients seemed to have acquired the penicillinase-producing gonococci in Liverpool. None admitted to recent sexual intercourse outside Liverpool. Another early case with a high MIC (more than 0.5 units per ml, enzyme not tested) in whom treatment failed with penicillin was that of a Nigerian. He had not left Liverpool since September 1975 and had had sexual intercourse in Liverpool, 12 days before attending the clinic; he denied any other sexual contact in the preceding weeks. Thus, the penicillinase-producing gonococci isolated in Liverpool could have arisen in Liverpool itself. As yet, the only other known possible source is Ghana. Nine gonococci isolated in America, and apparently acquired in the Far East, have been shown to possess plasmids of a molecular weight that was different from that of the three Liverpool isolates (Roberts and Falkow, 1977). However, the one isolated in London from a Ghanaian woman (Phillips, 1976), had a plasmid similar to that found in the Liverpool isolates. The London isolate and one from a Swedish sailor returning from Ghana were of the same auxotype as all the Liverpool isolates tested by one of us (AP). Therefore, it appears that all the Liverpool isolates were the same organisms and may prove to be identical with the two from Ghana, but there is no information about the time of emergence or prevalence of enzyme producing gonococci in Ghana to suggest their origin. Apparently none of the 80 isolates recently tested in Ibadan, Nigeria, was an enzyme producer (Osoba, 1977, personal communication).

CLINICAL FEATURES AND TREATMENT

In men, the few differences between those harbouring the penicillinase-producing gonococci and the rest—a shorter incubation period, slightly more severe symptoms, and a higher incidence of regional adenitis—suggest a greater tendency to local invasiveness. Only one patient with an enzyme positive strain developed disseminated infection.

We have not yet encountered a homosexual with rectal gonorrhoea caused by a penicillinase-producing gonococcus. One of the likely reasons is that most Black patients do not have rectal intercourse.

In women the symptoms and signs, including those suggesting salpingitis, were similar among the penicillinase-positive and penicillinase-negative categories. However, gonococci were isolated more often from multiple sites and this might indicate enhanced local invasiveness of penicillinase-positive gonococci.

While the treatment results with penicillin were as expected, the results of treatment with tetracycline in women were poor. The isolates were not fully sensitive to tetracycline (MICs 1 or 2 µg/ml). Serum levels in a group of women in Liverpool being studied by one of us (ER), receiving tetracycline 500 mg every six hours for chlamydial infection, rarely exceeded or even reached 2 µg/ml. For such relatively insensitive gonococci our results suggest that the failure rate with tetracycline is unacceptably high for women but not for men. Persistently positive post-treatment cultures from the rectum emphasise the necessity of taking tests from all potentially infected sites, otherwise one may miss not only the penicillinase-producing strains (Percival *et al.*, 1976) but also treatment failures in women.

The number of patients treated with the other regimens was small. However, spectinomycin and cefuroxime appeared to be effective in both men and women.

Control of the outbreak

Apart from one man seen at the end of November 1976 (included in Table 7), no new patient harbouring penicillinase-producing gonococci was seen until February 1977 when infection was discovered in a woman. There were two more cases in women in April. Consorts of two of these women were seamen who were not seen. They either could have reintroduced penicillinase-positive gonococci into Liverpool or the organisms might have remained asymptotically in them and been acquired earlier in Liverpool. The gonococcus was isolated in the third woman because her baby developed conjunctivitis shortly after birth. She was unmarried and claimed not to have had sexual intercourse for eight months. All three isolates were of the same auxotype as those in 1976.

During 1976 several patients, mainly women, had defaulted for long periods either untreated or with unknown outcome of treatment, despite intensive efforts in contact tracing, including up to 15 visits

Table 7 Relationship between no. of new and untreated patients infected by penicillinase-producing gonococci

Year	Month	New patients in each month		Cumulative numbers remaining untreated at end of each month	
		Total	Women	Total	Women
1976	February	10	2	4	
	March	8	4	5	4
	April	6	3	4	3
	May	8	2	2	1
	June	5	3	3	3
	July	15	4	6	3
	August	7	3	4	3
	September	10	6	6	6
	October	4	3	4	4
	November	4	2	3	2
	December	0	0	0	0
1977	January	0	0	0	0
	February	1	1	1	1
	March	0	0	0	0
	April	2	2	0	0
	May	0	0	0	0

to their homes. In Table 7, the number of new patients infected by penicillinase-producing gonococci each month is related to the cumulative numbers, at the end of the same month, of patients with enzyme positive gonococci who remained in Liverpool and were known to have been inadequately treated or were still untreated. It can be seen that the outbreak was apparently and at least temporarily controlled only when known cases had been effectively treated or the patient had left the area.

During the episode, 62% of declared consorts were traced and reported for treatment. Of the remaining 38%, some were probably treated at other clinics or at our clinics without an association with known cases being disclosed.

Four other factors may have contributed to limiting the outbreak. Firstly, in October, the change in second line treatment from tetracycline to cefuroxime as well as spectinomycin resulted in cures being achieved more quickly in women. Secondly, as most of the failures in women were confined to the rectum, theoretically at least, infectivity would be low in the absence of rectal intercourse, a practice believed to be rare in women. Thirdly, the gonococci could have spontaneously lost the plasmid determining production of penicillinase. In two patients only non-penicillinase-producing strains were isolated after treatment with penicillin and in one other this happened without any treatment, but it could have been a sampling error. Fourthly, unlike some of those found in the USA, Liverpool isolates do not carry the larger plasmid necessary for transfer of the penicillinase determining plasmid to other gonococci (Roberts and Falkow, 1977) as could occur in mixed infections.

Any long-term planning for the control of these strains cannot be separated from the control of gonorrhoea in general and possibly of other sexually transmitted diseases. A special situation, however, may be said to exist in some socially deprived areas of Liverpool with a predominantly immigrant and student population, which seems to be associated with the less sensitive and resistant strains of gonorrhoea. The relationship of venereal disease to adverse social phenomena is well known (Morton, 1973). Furthermore, a penicillinase-producing strain could at any time be reintroduced into an area by a traveller from other parts of the world where such strains continue to be common. Therefore, vigilance, appropriate treatment, and determined contact tracing must continue to remain the principal lines of defence.

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Addendum

Since this paper was submitted, two more cases, seen in Liverpool in January 1978, have been found to be infected with β -lactamase-producing gonococci. One, a woman with salpingitis, was infected by a Ghanaian seaman between October and December 1977 and the other, a Sudanese seaman acquired his infection in Port Sudan.

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